



Toxic epidermal necrolysis: the year in review

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Purpose of review

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening severe adverse drug reactions. Once thought to be idiosyncratic and unpredictable, there has been significant progress made in the understanding of the pathomechanism and pharmacogenetics of such reactions. These advances together with their clinical implications will be elaborated in this review.

Recent findings

It is now known that the human leukocyte antigen (HLA) association in SJS/TEN is more than just a genetic marker and has a functional role as well. This reaction is mediated by cytotoxic T lymphocytes (CTLs) in an HLA-restricted fashion. Certain drugs may bind directly to the HLA complex and facilitate the development of self-reactivity due to drug-modified HLA-peptide repertoire. The role of the drug-specific T cells and their T-cell receptors has also been clarified. Downstream cytotoxic signals have been elucidated with granulysin, a cytotoxic protein produced by CTLs or natural killer cells deemed to be the key mediator in the reaction.

Summary

Pharmacogenetic screening of HLA alleles prior to drug initiation has already been shown useful in the prevention of such reactions. The other advances in the disease mechanism will form the basis for better preventive and therapeutic strategies.

Keywords

granulysin, pharmacogenetics, Stevens–Johnson syndrome, toxic epidermal necrolysis

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, life-threatening reactions, which are characterized by epidermal detachment and mucositis. The majority of these reactions are caused by medications. Although a large spectrum of medications have been reported to cause SJS/TEN, the international case–control SCAR (severe cutaneous adverse reactions) [1] and the EuroSCAR study (European study of Severe Cutaneous Adverse Reactions) [2] have shown that certain drugs such as allopurinol, aromatic anti-convulsants, anti-infective sulphonamides, oxicam NSAIDs, lamotrigine, and nevirapine are associated with a much higher risk and the majority of reactions can be attributed to these medications [3[•]]. SJS and TEN are considered a disease continuum and are classified according to degree of epidermal detachment with body surface area (BSA) less than 10% considered SJS, greater than 30% as TEN, and 10–30% as SJS/TEN overlap. The incidence varies between five or six cases per million for SJS and one or two cases per million for TEN. Based on data collected in the RegiSCAR (International Registry of Severe Cutaneous Adverse Reactions to drugs),

the estimated mortality of SJS/TEN is 23% at 6 weeks and this increased to 34% at 1 year. Severity of the reaction influenced the mortality in the first 90 days, whereas the age and comorbidities influenced the mortality beyond 90 days and up to 1 year [3[•]]. Survivors of these severe reactions often have long-term sequelae, particularly affecting the eyes and mucocutaneous surfaces [4].

In the past, such reactions were thought to be idiosyncratic and unpredictable, but in recent years, there has been significant advancement in the understanding of the pathomechanism and pharmacogenetics of SJS/TEN. It is now known that there is a strong genetic association between human leukocyte antigens (HLAs) and specific

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KEY POINTS

- SJS/TEN is a specific immune reaction initiated by cytotoxic lymphocytes via an HLA-restricted pathway.
- A relevant HLA allele and TCR sequence are prerequisites for the reaction to occur.
- Certain drugs may trigger self-reactivity via the modification of the HLA-peptide repertoire.
- Granulysin is the key mediator of SJS/TEN.

drug-induced SJS/TEN, which makes screening a possibility. Recent studies have also clarified the pathomechanism, demonstrating the functional role of HLA markers, the specificity of T-cell receptors (TCRs), and the development of self-reactivity due to drug-modified HLA-peptide repertoire. Downstream cytotoxic signals have also been elucidated, demonstrating granulysin as the most important mediator. These recent advances will be elaborated in this review and their clinical implications discussed.

PHARMACOGENETICS

Various HLA alleles have been associated with SJS/TEN, but these associations are drug and ethnic-specific. These racial differences in genetic associations may be in part attributed to the variation in population frequencies of these alleles as well as the presence of other contributory genes. In SJS/TEN, the pharmacogenetics of carbamazepine (CBZ) and allopurinol has been the most studied and the observed strong association in Han Chinese and south-east Asia can be related to the high population frequency of HLA-B*1502 and HLA-B*5801.

Carbamazepine and other aromatic antiepileptics

Since the initial report of HLA-B*1502 and SJS/TEN in Han Chinese in Taiwan [5], this association has been replicated in other Asian countries, including Thailand, Hong Kong, Malaysia, China, and Indian ethnicities [6]. In white populations, the frequency of HLA-B*1502 is much lower and the link to CBZ-induced SJS/TEN is also more tenuous. Lonjou *et al.* [7] evaluated 12 patients with CBZ-induced SJS/TEN, only four patients carried the HLA-B*1502 allele, and all had Asian ancestry, suggesting that in white populations, other at-risk allele might be present. In addition to HLA-B*1502, other members of HLA-B75, which may share similar structural homology as HLA-B*1502 have been identified in CBZ-induced

SJS/TEN in other populations. This includes B*1508 in Indians [8], B*1511 in Thai and Japanese [9,10], B*1518 in Japanese [11], and B*1521 in Thai [6]. HLA-A*3101 was shown to associate with CBZ-induced nonbullous cutaneous adverse drug reactions [ADRs; maculopapular exanthema (MPE) or drug-induced hypersensitivity syndrome (DIHS, also known as DRESS)] in Chinese [12]. Recently, it has been suggested that HLA-A*3101 may be linked to all types of CBZ-induced cutaneous ADR (which includes MPE, DRESS, and SJS/TEN) in Japanese [13] and Europeans [14]. However, a recent international study [15] with a larger sample size showed that HLA-A*3101 is only linked to CBZ-induced DRESS and not CBZ-induced SJS/TEN. It has been known that cross-reactivity exists between the various aromatic antiepileptics; hence, it is not surprising that a similar linkage to HLA-B*1502 has been found in phenytoin-induced and oxcarbazepine-induced SJS/TEN [16,17]. However, the strength of association of HLA-B*1502 with phenytoin or oxcarbazepine-induced SJS/TEN is much weaker than that of CBZ, indicating other genetic or nongenetic factors may also contribute to the pathogenesis. In the case of lamotrigine, studies have been conflicting and no definite association can be made [17,18].

Allopurinol

The link between HLA-B*5801 and allopurinol SCAR was first reported by Hung *et al.* [19] as the allele was found in 100% (51/51) of patients with allopurinol SCAR but only 15% (20/135) in controls. Similar findings have been seen in Thai [20] and Korean [21,22] patients wherein all allopurinol cases were 100 and 80% carriers of HLA-B*5801 alleles, respectively. In other ethnicities, the association was more modest. In whites, 15 of 27 (55%) of patients with allopurinol SJS/TEN carried the HLA-B*5801 allele, wherein 1.5% of controls were positive [23]. In Japan, 40% of cases were positive for the allele compared with 0.1% of healthy controls [24]. A recent meta-analysis on the association between HLA-B*5801 and allopurinol-induced SJS/TEN identified nine studies up to June 2011 (four studies used case-matched controls; five used population controls). SJS/TEN cases were found to be significantly associated with HLA-B*5801 allele in both groups of studies with an odds ratio (OR) 96.6 (95% confidence interval, CI 24.5–381) in matched-control and OR 79.3 (95% CI 41.5–151.4) in population controls. Subgroup analysis between Asian and non-Asian populations yielded similar findings [25]. Two recent genome-wide association studies of SJS/TEN in Europe and Japan have

Table 1. Pharmacogenetics of human leukocyte antigen-associated Stevens–Johnson syndrome and toxic epidermal necrolysis

Drug	HLA allele	Ethnicity	References
Allopurinol	B*5801	Han Chinese, Thai, Koreans, Japanese, European	[19–24]
Carbamazepine	B*1502	Han Chinese, Indians, Europeans, Thai	[6,7,8,10,28]
	B*1511	Korean, Japanese	[9]
	B*1518, B*5901, C*0704	Japanese	[11]
Lamotrigine	A*3101	Han Chinese, Japanese, Europeans*	[12–14]
	B*1502; B*38; B*5801, A*6801, Cw*0718, DQB1*0609, DRB1*1301	Han Chinese, Europeans, Europeans	[17,23,29]
Methazolamide	HLA-B*5901, HLA-CW*0102	Korean, Japanese	[29]
Oxicam	B*73; A*2, B*12	European	[23,30]
Oxcarbazepine	B*1502	Han Chinese	[17]
Phenytoin	B*1502	Han Chinese, Thai	[17,31,32]
Sulfamethoxazole	A*29, B*12, DR7	European	[30]

HLA, human leukocyte antigen.

confirmed the importance of the HLA-B locus in allopurinol, with significant single nucleotide polymorphisms (SNPs) being located on chromosome 6 where the HLA-B genes are situated [26,27].

A summary of the pharmacogenetics of various HLA-associated SJS/TEN is shown in Table 1 [6–14, 17,19–24,28–32].

DRUG–HUMAN LEUKOCYTE ANTIGEN-EFFECTOR CELLS INTERACTION

Traditionally, various models have been proposed for the mechanism of immune-mediated ADRs. The hapten model proposes that drugs/or their metabolites are too small to elicit an immunogenic reaction on their own. Instead, they act as haptens which form covalent bonds with host peptides and are subsequently presented by the HLA to the TCR according to the classical peptide antigen pathway. A second model, the P-I model (direct pharmacological interaction) proposes that a drug/metabolite initiates immune reaction via a direct and reversible interaction with the TCR and peptide-loaded HLA without the need for prior metabolism. This direct interaction without the need for processing pathway was recently demonstrated in the CBZ-SJS/TEN model, in which it was shown that HLA-B*1502 loaded with endogenous peptides were able to bind CBZ directly without the involvement of intracellular drug metabolism or an antigen-processing pathway [33].

An alternative hypothesis, the ‘altered self-repertoire’ has recently been proposed. In this model, it is postulated that the binding of a drug to the HLA

molecule alters the specificity of the antigen-binding cleft, allowing a new repertoire of endogenous self-peptides to be bound and presented, resulting in an alloreactive CD8⁺ T-cell response. Three independent groups have recently validated this model using the example of abacavir drug hypersensitivity [34–36]. The binding of abacavir to the antigen-binding cleft of HLA-B*5701 resulted in alteration of the stereochemistry of the antigen-binding cleft. This alteration sterically hindered the binding of the normal repertoire of peptides and allowed for the binding of a new repertoire of peptides containing immunogenic neoepitopes. In addition, Illing *et al.* [34] also suggested that a similar process is at work in CBZ-SJS/TEN associated with HLA-B*1502. However, this model is unable to explain entirely what is observed in clinical practice. The altered self-repertoire model proposes that the drug alters the peptide repertoire in every carrier of the risk allele (~8% of the Han Chinese carries the HLA-B*1502 allele), but the prevalence of CBZ-SJS/TEN is very low (<0.1% of new users) and there are about 7% of tolerant CBZ users who carry the risk allele, HLA-B*1502, suggesting that other factors are necessary for the reaction to occur.

EFFECTOR CELLS AND RECEPTORS IN STEVENS–JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

It is well known that in SJS/TEN, the effector cells are the cytotoxic CD8⁺ T cells as well as natural killer (NK)/T cells and NK cells, being found abundantly in the blister fluids [37,38]. The link between these

cytotoxic T cells, HLA molecules, and the drug has been recently clarified. In Han Chinese, the negative predictive value of HLA-B*1502 for CBZ-SJS/TEN is 99.9%, whereas the positive predictive value is relatively low at 5.6%. Therefore, the majority of patients with HLA-B*1502 do not go on to develop SJS/TEN even when they are exposed to the drug. Utilizing the CBZ-SJS/TEN model, Ko *et al.* [39^{***}] demonstrated that a relevant TCR sequence on the cytotoxic T cell, in addition to the HLA-B*1502 model is required for the reaction to occur. The team demonstrated that in patients with CBZ-SJS/TEN, there was a skewed T-cell repertoire with a limited number of TCR clonotypes shared by the patients. VB-11-isgysy was identified as the predominant clonotype, being present in 16 out of 19 patients with SJS/TEN and was absent in all 17 drug-tolerant controls. In addition, in a minority of nonexposed controls carrying the HLA-B* 1502 allele, the presence of a certain TCR clonotype (VB-11) was predictive of in-vitro reactivity to CMZ. This study has clearly shown that in addition to specific HLA alleles, relevant TCR clonotypes are a prerequisite for SJS/TEN to occur.

MEDIATORS OF KERATINOCYTE APOPTOSIS

Although various cytotoxic proteins and cytokines such as soluble Fas ligand, perforin/granzyme, tumor necrosis factor- α (TNF- α), and TNF-related apoptosis-inducing ligand were previously proposed as mediators for the extensive keratinocyte apoptosis in SJS/TEN, it is now widely accepted that granulysin, a cytolytic protein found in cytotoxic T cells, NK/T cells, and NK cells is the most important mediator. Using gene expression profiling data, Chung *et al.* [38] demonstrated that granulysin was the most highly expressed cytotoxic molecule, and concentration of granulysin was two to four orders of magnitude higher than the concentrations of other mediators such as perforin, granzyme B, and soluble Fas ligand. In a cell model, depletion of granulysin reduced the cytotoxicity of the cells and in an in-vivo mouse model, the injection of granulysin into the skin replicated features of SJS-TEN.

THE ROLE OF THE INNATE IMMUNE SYSTEM IN STEVENS–JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

During the acute phase of SJS/TEN, there is a transient increase in the expression of several alarmin genes/or endogenous damage-associated molecular

patterns [40]. Alarmins are endogenous molecules that signal tissue and cell damage and several of these are increased in SJS/TEN including α -defensin 1–3 [41]. The exact function of these alarmins is unclear, but they may be involved in augmenting the immune reaction in SJS/TEN. In addition, degranulation and release of granulysin by NK cells/cytotoxic T cells may be influenced by the interaction of the innate receptor CD94/NKG2C expressed on NK cells/cytotoxic T lymphocytes and the HLA-E expressing keratinocytes [42].

CLINICAL IMPLICATIONS/UPDATES

The clinical implications from the aforementioned advances in pharmacogenetics and pathomechanisms are discussed below.

Pharmacogenetic screening

Screening and personalized drug therapy are the holy grail of pharmacogenetics research; however, before such tests become widely adopted, various factors including the medical need (i.e. the at-risk population and the preventable morbidity/mortality), the strength of pharmacogenetic association, the usefulness in therapeutic decision-making (dose alteration, alternative treatment, monitoring), as well as cost-effectiveness need to be considered [43[■],44]. The argument for HLA-screening in order to prevent SJS/TEN is particularly compelling based on its high mortality, the strong association particularly in certain drugs, and the availability of other therapeutic agents if a patient possesses the at-risk allele. The usefulness of HLA screening in preventing morbidity has been validated in the case of HLA-B*1502 and CBZ SJS/TEN in Han Chinese as well as HLA-5701 and abacavir drug hypersensitivity in whites [45,46]. However, these tests are probably less useful in other ethnic groups in which the alleles are associated with lower risk or in which other distinct HLA alleles are present. Recent guidelines on various HLA genotypes and their specific drug such as allopurinol and abacavir have been published [47,48].

Therapeutics and early diagnosis

The mainstay of treatment for SJS/TEN is still early withdrawal of the culprit drug, management in a specialized center, and supportive care. Based on its pathogenesis, various treatments including corticosteroids, intravenous immunoglobulin (IVIG), cyclosporine, cyclophosphamide, and TNF inhibitors have been proposed. IVIG is widely used and the

basis of its use in SJS/TEN is via the blocking of the Fas-Fas ligand interaction, thereby abrogating keratinocyte apoptosis. A recent meta-analysis did not demonstrate a significant difference in the pooled risk for mortality in patients treated with IVIG versus supportive care [49[¶]]. This is not surprising based on the findings of granulysin as the most important mediator in SJS/TEN compared with other mediators such as soluble Fas ligand and perforin/granzyme. In addition, granulysin may be an effective biomarker correlating to severity [38] as well as a tool to differentiate exanthematous drug reactions from early SJS/TEN [50,51].

The role of systemic corticosteroids is controversial; earlier studies in burns centers were associated with higher mortality, but a recent retrospective study [52] based on a large cohort of patients recruited in the EuroSCAR study found a trend toward a beneficial effect. Up to 15% of patients with SJS and TEN occur in patients who might be receiving concurrent chronic glucocorticoid therapy; the course of disease and outcome in these patients may provide indirect evidence on the usefulness of corticosteroids as therapy. In a recent case-control analysis of patients selected from the EuroSCAR/RegiSCAR studies, it was shown that long-term corticosteroids prior to the onset of disease may prolong the latency (time from drug initiation to onset of disease) and progression of disease but does not influence severity or mortality [53]. Cyclosporine has anti-inflammatory and immunosuppressive effect and an open trial of cyclosporine has been found to be useful [54]. Nonetheless, multicentered, controlled studies are needed to evaluate conclusively the usefulness of these specific therapies.

Drug imputability and in-vivo testing

Drug imputability/causality analysis in SJS/TEN is a challenge. Although SJS/TEN is predominantly due to medication, it must be recognized that in a proportion of cases, no drug culprit may be found and infections might be the trigger. Moreover, the current role of available in-vitro tests and skin tests is limited and drug challenge is contraindicated. The positivity of patch testing, though safe, generally approximates 25% [55[¶]]. However, patch test positivity also varies with type of drug tested. Allopurinol is frequently negative, in contrast to CBZ-induced SJS/TEN, in which up to 62.5% of patients demonstrate positive CBZ patch tests as well as cross-reactivity to other aromatic antiepileptic drugs (AEDs) [56] suggesting that other factors such as genetic factors (e.g. HLA-B*1502) and drug

factors (e.g. antigenicity of parent drug versus metabolite, skin penetrance) may also influence skin reaction on patch testing. The current role of in-vitro tests such as the lymphocyte transformation assay is still limited. Positive results vary between 11 and 21% depending on when the test was performed [57].

With the improved understanding of the pathomechanisms of SJS/TEN, newer in-vitro tools such as cytotoxic assays or elispot to various cytokines (e.g. IFN- γ and IL-4) may prove to be superior to lymphocyte transformation tests [58,59]. Until such tests become readily available and validated, it is important to assess causality based on drug history, temporal relationship, and epidemiological risks. An algorithm has been recently validated based on the results of the Euro-SCAR study and should be considered a useful tool in drug causality analysis [60].

CONCLUSION

In the last few years, there have been great strides made in the understanding of SJS/TEN. Key to this is the identification of pharmacogenetic markers, the clarification of HLA-drug-TCR interactions, and the identification of granulysin as the key mediator. With this advancement, further clinical applications, for example, screening, biomarkers, in-vitro tests, and targeted treatment are to be anticipated.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 452–453).

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